

Collagen type III to type I propeptides ratio is a better indicator of early-onset preeclampsia than a single propeptide

Collagen type III to type I propeptides ratio- an early onset preeclampsia indicator

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Abstract

Aim: In this study, we aimed to investigate whether maternal serum levels of collagen propeptides N-terminal propeptide of collagen type III (PIIINP), N-terminal propeptide of collagen type I (PINP) and C-terminal propeptide of collagen type I (PICP) warrant further study as candidate biochemical markers for the development of early-onset preeclampsia. **Material and Methods:** The sera of 32 patients with early-onset preeclampsia (≤ 34 gestational weeks) were examined. The mean age of the patients was 28.8 ± 5.5 years; and the mean age of 22 age-matched normal pregnant women was 28.5 ± 6.0 years. The enzyme-linked immunosorbent assay (ELISA) was used for measuring collagen type I and III propeptides- PIIINP, PINP, and PICP.

Results: Serum levels of PIIINP in women with preeclampsia were significantly higher than in normal pregnancies (150.3 ± 31.0 vs. 120.6 ± 29.5 $\mu\text{g/L}$) ($F=6.47$; $p=0.016$). There were no significant differences between levels of PINP and PICP in preeclampsia women than normal pregnancies (18.7 ± 5.5 vs. 18.8 ± 6.7 $\mu\text{g/L}$) ($p>0.05$) and (10.9 ± 3.8 vs. 10.5 ± 2.9 $\mu\text{g/L}$) ($p>0.05$) respectively. Although type I procollagen levels were not significantly elevated in preeclampsia, the ratio of type III to type I procollagen in sera of patients with preeclampsia was significantly higher than normal pregnancy (PIIINP/PICP= 13.8 vs. 11.5 ($t=-2.01$; $p=0.04$)).

Discussion: Our data suggest an association between changes in levels of PIIINP and the development of early-onset preeclampsia. Determination of the PIIINP/PICP ratio may be a more useful method for monitoring the development and progression of early-onset preeclampsia than a separate collagen propeptide marker.

Keywords

Collagen Type I; Collagen Type III; Propeptide; Biomarkers; Preeclampsia

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Introduction

Hypertension is one of the most widely seen disorders during pregnancy. Data show that hypertension complicates about 2-3% of pregnancies [1]. Hypertension in pregnancy is classified in preexisting hypertension, gestational hypertension, preeclampsia, preexisting hypertension plus superimposed gestational hypertension with proteinuria and antenatally unclassifiable hypertension [2]. Preeclampsia (PE) is a major cause of maternal and perinatal morbidity and mortality. Despite that fact, it has not been fully studied yet.

Preeclampsia is an important pregnancy complication. However, little is known about the change in the composition of the extracellular matrix (ECM) in the human uterus during preeclampsia. The uterine wall consists mainly of collagen types I and III. Derived products from their turnover: amino-terminal and carboxy-terminal propeptides circulate in the serum of patients with preeclampsia. The ECM is considered to play a pivotal role in the stability of tissue structure and the regulation of cell growth and differentiation. Collagen, fibronectin, and laminin are major components of the ECM of the human uterus. Collagen type I and type III are the main structural proteins of the uterine wall. The collagen structure of the uterus has been shown to be disturbed in women with preeclampsia.

It has been suggested that alterations in the composition of uterine ECM in preeclampsia might be similar to those of atherosclerosis or advanced aging. The possible cause of these changes might involve exposure to hypertension during pregnancy and an alteration in the density of human uterine cells. Cell density-dependent effects have been reported in a number of types of cells, such as mesangial cells, vascular smooth muscle cells, and fibroblasts. It has been suggested that cell density might modulate biological behavior, causing changes in signal transduction responses to hormonal stimulation, in the growth, synthesis, and composition of the ECM. The human placenta of preeclampsia is characterized by markedly increased relative levels of type V and type I collagens. Data show that alterations in placental collagen structure in preeclampsia might play an important role in the disturbance of trophoblastic cell functions and the supply of nutrients to the developing fetus necessary for the maintenance of pregnancy [3].

Collagen turnover is a dynamic process. Markers of its synthesis and degradation could be found in sera. Collagen synthesis markers include N-terminal propeptide of collagen type I (PINP), N-terminal propeptide of collagen type III (PIIINP) and C-terminal propeptide of collagen type I (PICP) [2]. Circulating PICP concentrations are considered to be reliable biochemical markers of bone formation [3,4].

Collagen types I and III are the main proteins involved in the structure of the uterine wall. As the uterus grows during pregnancy there is an intensified collagen turnover. It is well known that the uterine collagen structure has been shown to be disturbed in women with pre-eclampsia. Amino-terminal and carboxy-terminal propeptides of collagen type I and III play a central role in this process [4]. The human uterus is composed of a fibrous tissue framework consisting mainly of collagen types I and III. It is, therefore, possible that in hypertensive disorders in pregnancy these collagens (which are mainly responsible for

the coherence and supportive strength of the uterus) could be affected. Controlled collagenolysis and/or changes in collagen cross-linking will be needed to meet the demand of the growing uterine content to expand. As the uterus grows during pregnancy there is a high production and turnover of collagen proteins.

Type I collagen is fibrillar collagen and a major part of the interstitial membrane's structure. It is the most prevalent type of collagen and a key structural composition of many tissues. It is found practically in all structures involving connective tissue. "Type I collagen is the main structural protein of bone, skin, tendon, ligaments, sclera, cornea, blood vessels, as well as an important component of other tissues. It is gathered in fibers forming a structural-mechanical scaffold (matrix) of bones, skin, tendons, cornea, blood vessel walls, and other connective tissues. Heterotrimers of two $\alpha 1$ (I) and one $\alpha 2$ (I) chains are the dominant isoform of type I collagen. Homotrimers of three $\alpha 1$ (I) chains are found in fetal tissues and some fibrous lesions. The homotrimeric isoform is more resistant to cleavage than collagenases, which may explain its accumulation and functional role in tumors and fibrotic lesions" (Figure 1) [5].

Type III collagen is composed of one collagen α -chain, unlike most other collagens. This is a homotrimer containing three $\alpha 1$ (III) chains overlapped in a right triple helix. Type III collagen is secreted by fibroblasts and other types of mesenchymal cells, thus playing a major role in different inflammatory pathological conditions like lung damage, liver diseases, renal fibrosis, and vascular fibrosis diseases. Both collagen type III and type I are the main components of the extracellular matrix [6]. Type III collagen immunological biomarkers have been developed and widely used for the detection of fibrosis (Figure 1).

Collagen type I and III propeptides reflect collagen synthesis. According to the current knowledge, the most certain collagen type I and III turnover biomarkers with clinical and laboratory values are PINP, PIIINP, and PICP. All of them are collagen-derived peptides as PINP, PICP reflects collagen type I synthesis, while PIIINP reflects collagen type III synthesis. Their use as biomarkers with the prognostic or diagnostic aim in cardiovascular diseases is an area of intensive research. A small number of studies investigate collagen turnover in preeclampsia. There is a consensus that markers of collagen degradation could not be used as preeclampsia predictor biomarkers [7]. Scientific efforts should be focused on markers of collagen synthesis- the collagen propeptides. That is why the main focus of our study is indicators of collagen synthesis.

The objective of our study was to investigate whether maternal serum levels of collagen propeptides N-terminal propeptide of collagen type III (PIIINP), N-terminal propeptide of collagen type I (PINP) and C-terminal propeptide of collagen type I (PICP) warrant further study as candidate biochemical markers for the development of early-onset preeclampsia.

Material and Methods

Patients

All patients were residing in the vicinity of the Pleven University Hospital. Subjects' sera were taken from October 2019 to February 2020. All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the

Helsinki Declaration of 1975, as revised in 2000. The study was approved by a local Ethics Committee on 02/05/2019 with a number of 46. Informed consent from each participant was obtained too. The study group consisted of 32 patients with preeclampsia, the mean age of the patients was 28.8 ± 5.5 years; and the mean age of 22 age-matched normal pregnant was 28.5 ± 6.0 years (Table 1).

Criteria for inclusion in the study were as follows: pregnant women with clinical symptoms and laboratory criteria for early-onset preeclampsia (preeclampsia between 20 and 34 gestational week); maintaining a current diet and exercise during the study; signing informed consent to participate in the study; lack of metabolic syndrome and/or diabetes mellitus; parameters of hypertension (degree, stage, complications); presence/absence of risk factors; Presence/absence of target organs damage (brain, kidney, cardiac, ocular, peripheral); signed informed consent approved by the Ethics Committee at the University Hospital "G. Stranski" and the Medical University, Pleven.

Criteria for exclusion from the study were as follows: diabetes, kidney and heart disease, signs of chorioamnionitis, presence of a fetus with a chromosomal abnormality.

Diagnostic criteria for preeclampsia

Preeclampsia is defined by hypertension in pregnancy* and coexistence of one or more of the following new-onset conditions**:

***Definition and classification of hypertension in pregnancy according to the 2018 European Society of Cardiology (ESC) Guidelines for the management of cardiovascular diseases during pregnancy.**

The definition of hypertension in pregnancy is based only on office (or in-hospital) BP values (systolic BP (SBP) ≥ 140 mmHg and/or DBP ≥ 90 mmHg) and distinguishes mildly ($140/159/90-109$ mmHg) or severely ($\geq 160/110$ mmHg) elevated BP, in contrast to the grades used by the joint ESC/European Hypertension Society Guidelines (ESH) [8].

Definition of early-onset and late-onset preeclampsia according to ISSHP (International Society for the study of Hypertension in Pregnancy)

Early-onset preeclampsia (EOP) is defined before 34 weeks' gestation, and late-onset preeclampsia (LOP) is defined after 34 weeks or later [9].

****Proteinuria**

Spot urine protein/creatinine >30 mg/mmol (0.3 mg/mg) or >300 mg/day or at least 1 g/L ("2+") on dipstick testing.

****Other maternal organ dysfunctions**

(1) Renal insufficiency (creatinine >90 μ mol/L; 1.02 mg/dL); (2) Liver involvement (doubling of serum transaminases and/or severe right upper quadrant pain); (3) Neurological complications (eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus and severe headaches when accompanied by hyperreflexia and persistent visual scotomata); (4) Hematological complications (platelet count $<150,000$ /dL, DIC, and hemolysis).

****Uteroplacental dysfunction: Fetal growth restriction.**

Blood pressure

Arterial blood pressure was measured using a standard aneroid sphygmomanometer, to the nearest 2 mmHg, in the dominant arm after at least 10-min rest in the supine position. Blood pressure measuring was performed by the "Riester" blood pressure measuring tool- Type- Precisa® N; \varnothing 64 mm aluminium, Single-tube, Cotton hook cuff, adult, No.1362-104.

Electrocardiography

Electrocardiography (ECG) was performed for LVH assessment (Sokolow-Lyon index >35 mm, or R in aVL ≥ 11 mm; Cornell voltage duration product >2440 mm.ms, or Cornell voltage >28 mm in men or >20 mm in women) [10]. ECG was performed by 12-lead ECG machine "Fukuda"- Type- FX 8322.

Doppler of the uterine artery

Flow velocity waveforms of the uterine artery were performed by ultrasound apparatus using an AB 2-7 MHz convex abdominal probe. The mean pulsatility index (PI) was calculated. An abnormal Doppler of uterine artery result was diagnosed as a mean PI $>$ the 95th percentile for each gestational age [11].

ELISA

Enzyme-linked immunosorbent assay (ELISA) was used for measuring Collagen propeptides type I and III levels. They were measured in serum samples using enzyme-linked immunosorbent assay kits (RJ-HUFI00727, Human PIIINP/Procollagen III N-terminal Peptide, Reagent Genie), (RJ-HUFI00724, Human PICP/Procollagen I C-Terminal Peptide, Reagent Genie) and (RJ-HUFI00840, Human PINP/Procollagen I N-terminal Peptide, Reagent Genie) according to the manufacturer's instructions.

Statistical analysis

The research data were processed with the computer programs Excel (Microsoft Corporation, Redmond, WA) and Statgraphics Plus (Manugistics, Rockville, MD) for Windows. All results were described in tables, graphs, numerical values (mean \pm SD, share indicators, and correlations). The level of significance was determined as ($p < 0.05$). The one-way analysis of variance with the F-test in the ANOVA table was used for means comparison. The Kruskal-Wallis test was performed in cases different from a normal distribution. Median (M) was used in the Kruskal-Wallis test together with first and third quartile Q1 and Q3; (twenty-fifth and seventy-fifth percentile P25 and 75P). Student's T-Test was used to compare the means between two groups. The Pearson test was used for assessing correlations. Multivariate regression analysis was performed too.

Results

Serum levels of PIIINP in women with preeclampsia were significantly higher than in normal pregnancies ($150,3 \pm 31,0$ vs. $120,6 \pm 29,5$ μ g/L) ($F=6,47$; $p=0,016$) (Table 2); (Figure 2). There were no significant differences between levels of PINP and PICP in preeclampsia women than normal pregnancies ($18,7 \pm 5,5$ vs. $18,8 \pm 6,7$ μ g/L) ($p > 0,05$) and ($10,9 \pm 3,8$ vs. $10,5 \pm 2,9$ μ g/L) ($p > 0,05$) respectively. Although type I procollagen levels were not significantly elevated in preeclampsia, the ratio of type III to type I procollagen in sera of patients with preeclampsia was significantly higher than normal pregnancy (PIIINP/PICP= 13,8 vs. 11,5 ($t=-2.01$; $p=0.04$)) (Figure 3).

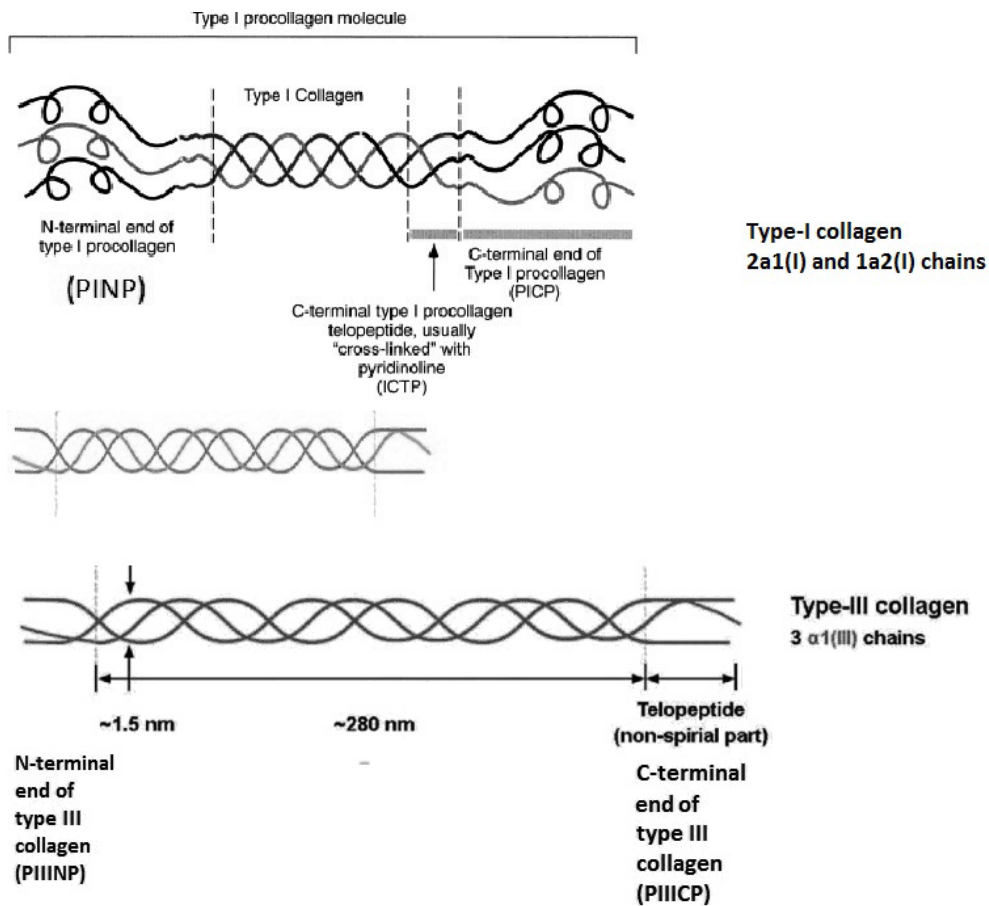


Figure 1. Collagen type I and type III structure

PICP-collagen-derived peptide including the carboxy- terminal peptide of procollagen type I formed on the extracellular conversion of procollagen type I into fibrillar collagen I

PINP-collagen-derived peptide including the amino-terminal propeptide of collagen type I

ICTP-telopeptide of collagen type I

PIIINP-collagen-derived peptide including the amino-terminal propeptide of collagen type III arising on extracellular conversion of procollagen III to fibrillar collagen III

Serum levels of PICP, PINP and PIIINP (µg/L)

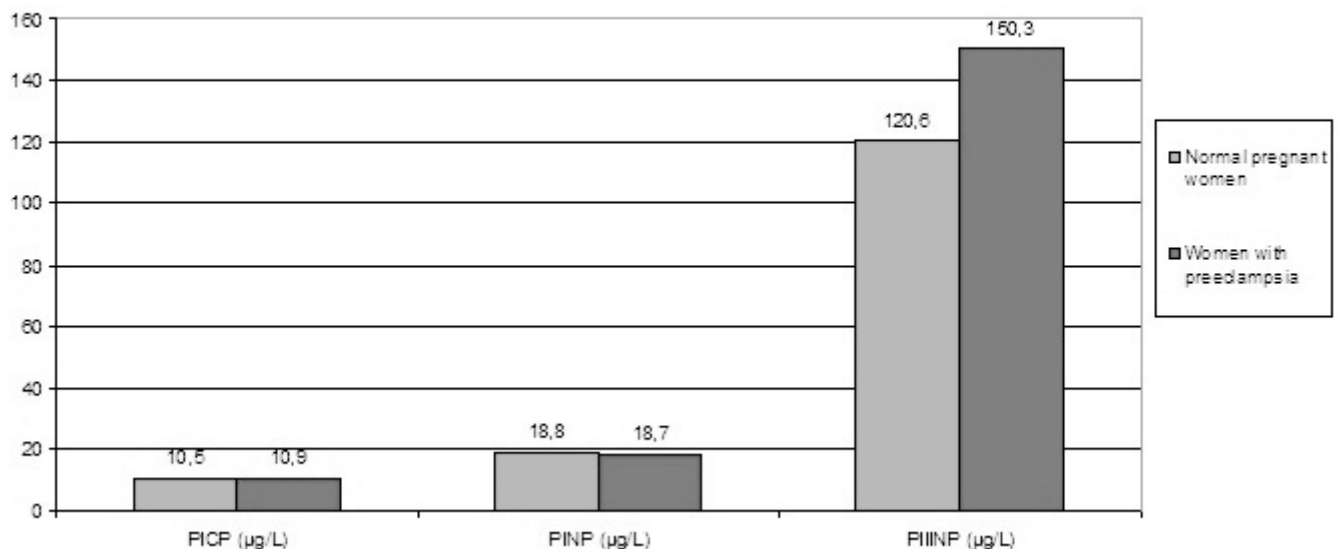


Figure 2. Serum levels of collagen type I and III propeptides levels in women with preeclampsia compared to normal pregnant women.

N-terminal propeptide of collagen type III (PIIINP); N-terminal propeptide of collagen type I (PINP); C-terminal propeptide of collagen type I (PICP)

PIIINP/PICP and PIINP/PICP ratios in normal pregnant women and women with preeclampsia

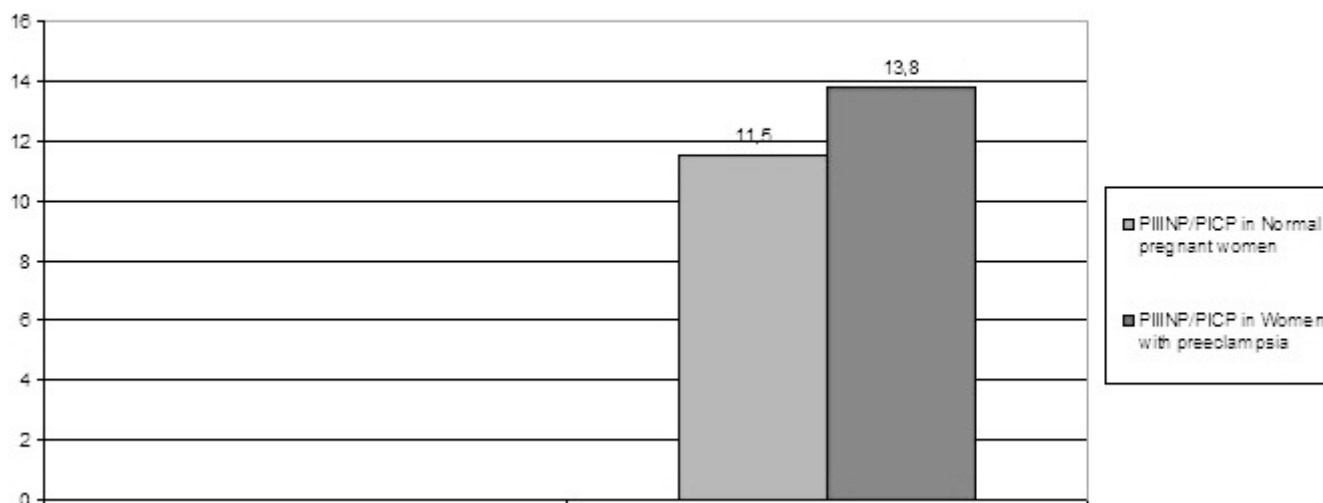


Figure 3. PIIINP to PICP ratio in women with preeclampsia compared to normal pregnant women. N-terminal propeptide of collagen type III (PIIINP); C-terminal propeptide of collagen type I (PICP)

Table 1. Clinical data of women with preeclampsia and normal pregnant women

	Preeclampsia	Normal pregnant women
Maternal age	28.8±5.5	28.5±6.0
BMI≥25	23/32*	4/22
Gravida	2(2)**	3(2) **
Parity	1(2) **	1(2) **
SBP (mmHg)	138±17*	116±14
DBP (mmHg)	81±10*	68±8
Past history of preeclampsia	1/32	8/22*
Family history of hypertension	11	19*
Chronic hypertension	1/32	10/22*
Abnormal UAD	18/32*	2/22
Smoker	6/32	2/22
Number	(n=32)	(n=22)

BMI- body mass index; SBP- systolic blood pressure; DBP- diastolic blood pressure; UAD- uterine artery Doppler; Data are shown as the mean±SD; *p<0,05; **Data are expressed as median (interquartile range)

Table 2. Serum levels of collagen type I and III propeptides levels in women with preeclampsia compared with normal pregnant women

Serum levels (µg/L)	PIIINP	PINP	PICP
Preeclampsia	150,3±31,0*	18,7±5,5	10,9±3,8
Normal pregnant women	120,6±29,5	18,8±6,7	10,5±2,9

N-terminal propeptide of collagen type III (PIIINP), N-terminal propeptide of collagen type I (PINP), C-terminal propeptide of collagen type I (PICP)

Discussion

Preeclampsia is one of the most common pregnancy disorders. Preeclampsia is characterized by a high blood pressure of mother, often with proteinuria. Fetal growth restriction is generally seen too. Early detection is paramount for risk stratification and prevention of further complications. There is growing evidence for collagen involvement in preeclampsia's pathophysiology. Even though collagen metabolism in preeclampsia is not fully studied yet, some of the possible reasons could be as follows: (1) usage of different laboratory methods for determination of serum collagen biomarkers like radioimmunoassay tests; (2) collagen measurement in different human specimens like blood, urine or placenta samples. Interestingly, almost all studies investigating collagen turnover in preeclampsia did not differentiate patients with early-onset preeclampsia (≤34 gestational weeks) from patients with late-onset preeclampsia (≥34 gestational weeks) and their conclusions are not based on this differentiation.

Despite the postulated early onset of the disease process of preeclampsia, this serious pregnancy complication is most often not diagnosed until the third trimester. There is an active search for biochemical markers to identify patients at high risk for preeclampsia development. Many candidate molecules are proposed in the literature. Various placental secretory products have been tested as potential markers of pre-eclampsia. Among these, insulin-like growth factor binding protein-1 (IGFBP-1; PP12), inhibin A, activin A and human chorionic gonadotropin (hCG) have been shown to be elevated 3–9-fold at the time of disease. Early identification of patients who are at higher risk to develop preeclampsia would aid in the development of the effective intervention. Studies' findings have suggested that maternal serum levels of peptides specific for the synthesis of collagen types I (procollagen I carboxy-terminal peptide, PICP) and III (procollagen III amino-terminal peptide, PIIINP) are significantly higher in preeclamptic versus control pregnancies

[4, 7].

Ogawa H et al. 1994 localized collagen types III and IV in the placenta by immunohistochemistry, and measured by radioimmunoassay other collagen-related substances such as the amnio-terminal peptide of type III procollagen (P-III-P) and type IV collagen 7S domain (7S) in the serum of pregnant women. "By means of immunohistochemical techniques, authors studied the localization of type III and IV collagen in normal and toxemic placentas. They also studied the maternal serum levels of type III procollagen peptide and type IV collagen 7S domain (7S) in non-pregnant women, normal term women, and cases toxemia of pregnancy. Immunohistochemical studies revealed that type III collagen exists in the connective tissues composing the villous core and type IV in the basement membranes of trophoblast cells and fetal vascular elements. Even in normal-appearing toxemic placenta, the amount of type III and IV collagen appeared to be increased compared with that in normal term placenta, but the amount of type III and IV collagen appeared to be decreased in the necrotized chorionic villi of severe toxemia. Measurement of the collagen-related substances revealed that those levels in toxemic pregnancy were much higher than those in normal term pregnancy. In toxemic pregnancy, the incidence of IUGR in the high type III procollagen level group was increased significantly and increased more apparently in both the high type III procollagen and 7S groups. Authors conclude that their data support type III procollagen and 7S in maternal serum flow from the necrotized chorionic villi into the intervillous space and that these measurements are significant indicators of placental damage caused by toxemia of pregnancy" [12].

Yamamoto H et al. in 2001 and Kanagasabai S et al. in 2009 [13,14] measured PICP and PIIINP by radioimmunoassay in maternal serum samples from patients diagnosed with pre-eclampsia at 32 weeks' gestation or later and in controls from the same period of gestation. For PICP, 37 cases and 36 controls were studied; for PIIINP, 12 cases and 19 controls were studied. The authors found that maternal serum levels of PICP and PIIINP are mildly elevated in patients with pre-eclampsia. These markers are unlikely to be useful in the prediction of pre-eclampsia.

Anim-Nyame N et al. in 2002 [15], found that C-terminal telopeptide of collagen type I (ICTP) and PICP increased progressively in the normal pregnant and pre-eclampsia groups, but the rate of increase was significantly greater in the latter ($P = 0.00002$ and 0.0008 , unpaired t-test, for ICTP (and PICP summary measures, respectively)).

Yasumizu T et al. in 1996 [16], measured serum PICP, ICTP, and osteocalcin in 17 full-term mother-infant pairs and 17 age-matched nonpregnant women. "Serum PICP and ICTP of term women at the time of delivery were significantly higher ($P < 0.025$, $P < 0.01$, respectively) and serum osteocalcin was significantly lower ($P < 0.001$) than in nonpregnant women. The ratio of PICP to ICTP was essentially the same for term and nonpregnant women. Serum PICP, ICTP, and osteocalcin were virtually the same in the umbilical arteries and vein. PICP, ICTP, and osteocalcin were much higher in fetal than maternal circulation ($P < 0.001$)".

It has been reported that the ratio of type V to type I collagen was significantly higher in term than in premature placentae.

This suggested a change in these ratios in the placenta during the process of development and aging [17]. In contrast, the ratio of type III to type I was lower, and that of type V to type I was higher, in placentae from preeclampsia compared with normal term placentae.

Pathological collagen type I turnover was found in the aorta, uterus, and placenta of pregnant rats with reduced uterine perfusion pressure (RUPP). RUPP is one of the main pathophysiological signs of preeclampsia. "Maternal blood pressure was higher and the litter size and pup weight were lower in RUPP compared with Preg rats. Gelatin zymography showed prominent uterine matrix metalloproteinases (MMPs) MMP-2 and MMP-9 activity that was dependent on the amount of loaded protein. At saturating protein loading, both gelatin and casein zymography revealed two additional bands corresponding to MMP-1 and MMP-7 that were greater in the aorta, uterus, and placenta of RUPP compared with pregnant rats. Western blots and immunohistochemistry confirmed increased MMP-1 and MMP-7 in the aorta, uterus, and placenta of RUPP versus pregnant rats. The levels of MMP-1 and MMP-7 substrate collagen type I were greater in tissues of RUPP compared with pregnant rats" [18].

The latter studies suggested that the procollagen peptides might serve as serum markers of preeclampsia development. The thorough analysis of data of all available studies of collagen metabolism in preeclampsia [12-18] shows that the extent of the elevation of each marker was mild to moderate. Authors conclude that it is less likely that PICP or PIIINP levels, measured in the second trimester, would be predictors of preeclampsia, although this remains to be tested. That is why we broadened our investigation and examined not only serum procollagen peptides concentrations themselves (PINP, PICP, PIIINP), but also their ratios- PIIINP/PINP and PIIINP/PICP. These markers were determined only in sera of women with early-onset preeclampsia (≤ 34 gestational weeks). Our results are consistent with previous findings; maternal serum levels of PICP and PIIINP (markers of type I and type III collagen metabolism) were elevated in pregnancies diagnosed with pre-eclampsia. We found that PIIINP levels were elevated to a greater extent than PICP levels and the ratio of type III to type I procollagen in sera of patients with preeclampsia was significantly higher than a normal pregnancy. Both data have not been reported yet in literature.

Despite the active search of multiple potential preeclampsia biomarkers, the clinical efficacy of these markers has shown low predictive value. The exact biological role of collagen pre-eclamptic pregnancy is not well fully defined yet [19-22].

In our study, we determined maternal serum levels of PICP, PINP, and PIIINP in women with normal pregnancy and early-onset preeclamptic pregnancies. We investigated whether these collagen propeptide markers warrant further study as candidate biochemical markers for the development of early-onset pre-eclampsia. Our findings showed that serum levels of PIIINP in women with preeclampsia were significantly higher than in normal pregnancies. Although type I procollagen levels were not significantly elevated in preeclampsia, the ratio of type III to type I procollagen in sera of patients with preeclampsia was significantly higher than a normal pregnancy.

This is a pilot study. To more precisely determine the extent of the association of these markers with concurrent pre-eclampsia, it would be necessary to conduct a larger prospective non-intervention trial.

Conclusions

There is an association between changes in levels of PIIINP and the development of early-onset preeclampsia. Determination of PIIINP/PICP ratio may be a better early-onset preeclampsia development indicator than a separate collagen propeptide marker.

Limitations

The small sample size is a limitation of the study design. In addition, there is a lack of actual literature that is related to our study topic.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. European Cardiology Society Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018; 39(34): 3165-3241.
2. Amaral L, Wallace K, Owens M, LaMarca B. Pathophysiology and Current Clinical Management of Preeclampsia. *Curr Hypertens Rep*. 2017; 19(8): 61-6.
3. Eiland E, Nzerue C, Faulkner M. Preeclampsia 2012. *J Pregnancy*. 2012; 2012:586578. DOI: 10.1155/2012/586578.
4. Pulkkinen MO, Lehto M, Jalkanen M, Nanto-Salonen K. Collagen types and fibronectin in the uterine muscle of normal and hypertensive pregnant patients. *Am J Obstet Gynecol*. 1984; 149(7):711.
5. Henriksen K, Karsdal MA. Chapter 1- Type I Collagen. *Biochemistry of Collagens, Laminins and Elastin Structure, Function and Biomarkers*. Karsdal MA, editors. 1st ed. Cambridge, MA, USA: Academic Press; 2016. p.1-11.
6. Nielsen MJ, Karsdal MA. Chapter 3- Type III Collagen. *Biochemistry of Collagens, Laminins and Elastin Structure, Function and Biomarkers*. 2nd ed. Cambridge, MA, USA: Academic Press; 2019. p.21-30.
7. Yamano H, Lambert-Messerlian GM, Silver HM, Kudo R. Maternal serum levels of type I and type III procollagen peptides in preeclamptic pregnancy. *J Matern Fetal Med*. 2001; 10(1): 40-3.
8. ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018; 39(33): 3021-3104.
9. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens*. 2014; 4(2) 97-104.
10. Lehtonen AO, Puukka P, Varis J, Porthan K, Tikkanen JT, Nieminen MS, et al. Prevalence and prognosis of ECG abnormalities in normotensive and hypertensive individuals. *J Hypertens*. 2016;34(5):959-66.
11. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, et al. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). *Eur Heart J Cardiovasc Imaging*. 2015;16(6):577-605.
12. Ogawa H, Hata T. Maternal serum type III procollagen peptide (P-III-P) and 7S domain of type IV collagen (7S) as indicators of placental damage caused by severe toxemia of pregnancy. *Trophoblast Research*. 1994; 8:367-81.
13. Kanagasabai S. Biochemical Markers In The Prediction Of Pre-Eclampsia, Are We There Yet? *Internet J Gynecol Obstet*. 2009;14(1): 1-8.
14. Yamamoto H, Lambert-Messerlian GM, Silver HM, Kudo R, Kellner LH, Canick JA. Maternal serum levels of type I and type III procollagen peptides in preeclamptic pregnancy. *J Matern Fetal Neonatal Med*. 2001;10:40-3.
15. Anim-Nyamea N, Soorannaa SR, Jonesb J, Alagband-Zadehb J, Steera PJ,

Johnsona MR. A longitudinal study of biochemical markers of bone turnover during normal pregnancy and pregnancies complicated by pre-eclampsia. *BJOG*. 2002; 109:708-13.

16. Yasumizu T, Kato J. Concentrations of serum markers of type I collagen synthesis and degradation and serum osteocalcin in maternal and umbilical circulation. *Endocr J*. 1996;43(2):191-5.

17. Iwahashi M, Ooshima A, Nakano R. Increase in the relative level of type V collagen in the placenta of patients with pre-eclampsia. *Mol Hum Reprod*. 1997; 3(8): 725-8.

18. Li W, Cui N, Mazza MQ, Mata KM, Khalil RA. Increased vascular and uteroplacental matrix metalloproteinase-1 and -7 levels and collagen I deposition in hypertension-in-pregnancy. Role of TNF- α . *Am J Physiol Heart Circ Physiol*. 2017;313(3):H491-H507.

19. Gupteccorresponding S, Wagh G. Preeclampsia-Eclampsia Review Article. *J Obstet Gynaecol India*. 2014; 64(1): 4-13.

20. Torres J, Faris I, Callejas A. Histobiomechanical Remodeling of the Cervix during Pregnancy: Proposed Framework. *Hindawi*. 2019; 1-11. DOI:10.1155/2019/5957432

21. Gallo M, Wright D, Casanova C, Campanero M, Nicolaidis K. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19-24 weeks' gestation. *Am J Obstet Gynecol*. 2016; 214(5): 6191-7.

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